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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,493	03/16/2004	Riqiang Yan	29915/00281E	2136

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EXAMINER	
MAHATAN, CHANNING S	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
09/14/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/801,493	YAN ET AL.	
	Examiner	Art Unit	
	CHANNING S. MAHATAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 16, 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *84,85,88-91,94-108 and 110* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *84, 85, 88-91, 94-108, and 110* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 16, 2010 has been entered.

Claims under Examination

Claims 1-83, 86, 87, 92, 93, and 109 have been canceled. Claims herein under examination are claims 84, 85, 88-91, 94-108, and 110.

Applicant's Arguments

Applicant's arguments, filed March 16, 2010, have been fully considered but they are not deemed persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Lack of Written Description

The rejection of claims 84, 85, 88-91, 94-108, and 110 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the claims do not have written description for the full breadth of the claims.

The summary of '*The Invention in General*' and '*The Claimed Invention*' in the *'Office Action*' (page 4, line 26 to page 5, line 20), mailed September 16, 2009, is herein reiterated.

Applicant's arguments in the '*Response*', filed March 16, 2010, and further clarification of the rejection are provided below.

Factual Inquiry of the Supporting Disclosure

In the '*Response*' (page 3, lines 4-7), filed March 16, 2010, Applicant argues that Table 6 on page 30 of the specification provides a summary of the specific amino acid residues that are preferred at the cleavage site-proximal positions within a substrate. On the basis of the previous factual inquiry and the following further factual inquiry of the disclosure, Applicant's argument is found unpersuasive.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed. See MPEP 213.

A factual inquiry of the instant disclosure was previously described in the '*Office Action*' (page 5-7; entitled: "*The Supporting Disclosure*"), mailed September 16, 2009, and is reiterated herein. To clarify the prosecution record and to further address Applicant's submission that support for the instantly claimed invention can be found in the instant specification at Table 6, Table 6 is as follows:

Table 6 depicts exemplary amino acids that will be useful at each of positions P_4, P_3, P_2, P_1, P_1' P_2' P_3' and P_4'

	P_4	P_3	P_2	P_1	↓	P_1'	P_2'	P_3'	P_4'
B_1	E	A	N	Y		E	V	E	F
B_2	G	V	L	L		A	A	G	W
B_3	I	I	K	M		D	N	F	G
B_4	D	S	S	Nle		M	T	H	A
B_5	T	H	G	F		Q	L	C*	H
B_6	C*	Y	T	H		S	F	S	P
B_7	S	T	D			G	S		G
B_8		F	A						N
B_9			Q						S
B_{10}			E						E

C* refers to Cysteic Acid

The description of Table 6 appears to suggest merely prophetic amino acids at the corresponding positions in a sequence, via the recitation of the language "exemplary amino acids that will be useful at each of positions P_4, P_3, P_2, P_1, $P_{1'}$, $P_{2'}$, $P_{3'}$, and $P_{4'}$". The disclosure lists and describes 199 SEQ ID NOs (see '*Sequence Listing*' and instant specification), however, none of these sequences appear to describe the claimed amino acid sequence "NF-EA." Further, the none of the 199 SEQ ID NOs appear to indicate at least three (3) of the claimed amino acid sequence (i.e. NF-E_; NF-_A; N_-EA; and _F-

EA). At most only two (2) amino acids (underlined below) of the claimed "NF-EA" amino acid sequence are present:

SEQ ID NO: 5	KVEANY-EVEGERKK (also refer to Tables 2 & 3)
SEQ ID NO: 19	SEVNL-DAEFR (also refer to Tables 1 & 4)
SEQ ID NO: 34	SSNF-AVGA (also refer to Table 1)
SEQ ID NO: 49	•ANY-EVEF
SEQ ID NO: 50	E▼NY-EVEF
SEQ ID NO: 51	EA◄Y-EVEF
SEQ ID NO: 52	EAN♦-EVEF
SEQ ID NO: 53	EANY-◊VEF
SEQ ID NO: 54	EANY-EΔEF
SEQ ID NO: 55	EANY-EV▷F
SEQ ID NO: 56	EANY-EVEΔ
SEQ ID NO: 133	KTINL-EVEPS (also refer to Table 3)
SEQ ID NO: 134	KTINnle-EVEPS (also refer to Table 3)
SEQ ID NO: 135	KTINnle-EVDPS (also refer to Table 3)
SEQ ID NO: 142	NL-DA
SEQ ID NO: 144	SEVSY-EAEFR (also refer to Table 4)
SEQ ID NO: 187	SY-EA

The specification further states that "[i]t is envisioned that peptides may be constructed from the above table that have for example at position P_1, any of amino acids B_1 through B_7 in the P_1 column" (page 30, lines 18-21).

In such instances the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention. *Id.*

Accordingly, the above factual inquiries of the instant disclosure demonstrates the factual uncertainty of possession for the amino acid sequence “NF-EA” and/or for at least three (3) of the amino acid sequences similar to "NF-EA".

Level of Skill in the Art

In the '*Response*' (page 3, lines 4-7), filed March 16, 2010, Applicant argues that Table 6 is “not a ‘laundry list’ of ‘every possible moiety’” but rather a “shorthand way of listing specific permutations that the inventors contemplated as the invention”. The “*Declaration of John P. Anderson”*, filed March 16, 2010, purports that "[t]he reader understands Table 6 to provide a concise description of each of the 10x6x7x7 = 2,940 peptide substrates defined by independently selecting $P_2P_1P_{1'}P_{2'}$ from the choices provided in the Table" (page 6, line 23 to page 7, line 2). Further, it is noted that the disclosure provides for only 199 SEQ ID NOs (see “*Sequence Listing”*). Applicant's argument is found unpersuasive as discussed below.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("*If* n-propylamine had been used in making the compound instead of n-butylamine, the

compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original); *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) ("the specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio... to be part of their invention .... There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

A reader of would understand that Table 6 "depicts exemplary amino acids that will be useful at each of positions $P_4P_3P_2P_1P_{1'}P_{2'}P_{3'}P_{4'}$", wherein Table 6 lists amino acids for positions $P_4P_3P_2P_1P_{1'}P_{2'}P_{3'}P_{4'}$ (see above "*Factual Inquiry of the Supporting Disclosure*"). Subsequently, a reader could then calculate the different possible amino acid sequence combinations based upon the listed amino acids and corresponding positions in Table 6, which would yield 9,878,400 possible sequences wherein P_4 is 7, P_3 is 8, P_2 is 10, P_1 is 6, $P_{1'}$ is 7, $P_{2'}$ is 7, $P_{3'}$ is 6, and $P_{4'}$ is 10 (7x8x10x6x7x7x6x10 = 9,878,400 sequences). Applicant's characterization of Table 6 as "a shorthand way of listing specific permutations", thus, appears overly generous (9,878,400 sequences versus 2,940 sequences) and at odds with the disclosed Table 6 ($P_4P_3P_2P_1P_{1'}P_{2'}P_{3'}P_{4'}$ versus $P_2P_1P_{1'}P_{2'}$). Similarly to the conclusion reached in *Fujikawa*, Applicant's

"contemplated" amino acid sequences table listing (having possible combination of 9,878,940 different sequences) does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. For instance, the selection of the particularly claimed "NF-EA" amino acid sequence from the possible 9,878,400 sequences (or even out of 2,940 sequences, as asserted by Applicant), in the absence of even closely related amino acid sequences (i.e. NF-E_; NF-_A; N_-EA; and _F-EA), appears to indicate for one to randomly select an amino acid sequence.

With respect to the level of disclosure of the "NF-EA" amino acid sequence, it is acknowledged that the "NF-EA" amino acid sequence need not be disclosed in exact detail (*ipsis verbis*), but must be at a level for a skilled artisan to have understood that the inventor was in possession of the claimed invention at the time of filing. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.") If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d

746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of skill in the art would reasonably afford Applicant possession of the amino acid sequence “NF-EA” in the disclosure if the following sequences were found to demonstrate cleavability by human aspartyl protease in the specification: 1) NF-E_; 2) NF-_A; 3) N_-EA; and 4) _F-EA. However, the specification fails to describe the instantly claimed "NF-EA" amino acid sequence or an at least three (3) amino acid sequence that is cleavable by human aspartyl protease. In fact the disclosure and instant claim 84 appears to teach/direct one of skill in the art not to select particular amino acids for P_2P_1-$P_1'P_2'$. The instant specification (page 3, line 24 to page 5, line 9) and instant claim 84 indicate/recite the limitation "wherein the peptide does not comprise the corresponding P_2P_1-$P_1'P_2'$ portion of amino acid sequence depicted in SEQ ID NO: 19,...SEQ ID NO: 34”. However, the P_2P_1-$P_1'P_2'$ portion of amino acid sequence of SEQ ID NOs: 19 and 34 appears to directly conflict (underlined below) with a portion of the instantly claimed “NF-EA” amino acid sequence, wherein SEQ ID NO: 19 is NL-DA and SEQ ID NO: 34 is NF-AV. In the absence of "full, clear, concise, and exact terms" for “NF-EA”, it would appear that one of skill in the art would not have acknowledged or deduced that Applicant was in possession of “NF-EA”, when portions of the claimed amino acid sequence conflict with those that are indicated as not the amino acid sequence.

State/Knowledge of the Art

Applicant reiterates the argument in the '*Response*' (page 3, line 20 to page 4, line 5), filed March 16, 2010, and the '*Declaration of John P. Anderson*' (page 19, lines 5-21, that post-filing publication International Patent Publication No. WO 02/094985 confirms that substrates having a core defined as P_2 is N; P_1 is F; $P_{1'}$ is E; or $P_{2'}$ is A, are cleaved 17 times more efficiently than the Swedish mutation". Applicant further argues in the '*Response*' (page 4, lines 23-26) and in the '*Declaration of John P. Anderson*' (page 15, line 17 to page 19, line 4), when viewed as a whole, the previously cited references (Gruninger-Leitch et al.; Majer et al.; Sauder et al.; Tomasselli et al.; and Shi et al.) along with additional references (Oliveiria et al. and Andrau et al.) "demonstrate that the vast majority of the peptide substrates disclosed in Table 6 of the patent application will be cleaved by β-secretase and the core amino acids are far more important to peptide cleavage as compared to residues at positions more distant from the cleavage site".

It is acknowledged that WO 02/094985 describes the amino acid sequence NF-EV, wherein at least three (3) amino acids are the same and similarly positioned (SEQ ID NO: 262 in Table 3) as the instantly claimed amino acid sequence "NF-EA". The fact is WO 02/094985 is post-filing art and does not resolve the deficiency of the instant application for demonstrating possession of the amino acid sequence "NF-EA" at the time the invention was filed. Applicant's assertion that "WO 02/094985 also provides confirmation of sufficient disclosure of β-secretase substrates" appears to support the position that certain issues were still not resolved or did not overcome the unpredictability that results in undue experimentation.

None of the cited references (Gruninger-Leitch et al.; Majer et al.; Sauder et al.; Tomasselli et al.; and Shi et al.; Oliveiria et al.; and Andrau et al.) "as a whole" resolve the lack of written description in the instant specification. None of these references disclose a well-established correlation between structure and function of the instantly claimed amino acid sequence "NF-EA". Accordingly, in view of the instant specification the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Compare *Fonar*, 107 F.3d at 1549, 41 USPQ2d at 1805 (disclosure of software function adequate in that art). Furthermore, disclosure of a partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention. See, e.g., *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021 ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.")

Accordingly, for at least these reasons, Applicant has not adequately described the invention for the breath that is claimed. Thus, it appears that Applicant was not in possession of the claimed invention at the time the application was filed, the structure-function relationship between the protease and the scissile substrates have not been adequately set forth, and that Appplicant's species do not support the claimed genus.

New Matter

The rejection of claims 84, 85, 88-91, 94-108, and 110 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as stated above (see '*Lack of Written Description*') is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 84 and all claims dependent therefrom have been amended to recite "P_2 is N; P_1 is F; $P_{1'}$ is E; and $P_{2'}$ is A" which is considered new matter. As discussed above ('*Lack of Written Description*') the instant specification fails to provide adequate support for the claimed substrate. Therefore, the above amendment is considered NEW MATTER.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to CHANNING S. MAHATAN whose telephone number is (571)270-7464. The Examiner can normally be reached on Monday - Thursday; 7:30am-5pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CHANNING S MAHATAN
Examiner
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